and TCD-BM in absence of FLU (P = .01); recipient CMV seronegative status (93% vs 69%, P = .02); HLA matched donor-recipient pair (94% vs 69%, P = .01); negative transfusion history (100% vs 83%, P = .05), and use of FLU in the preparative regimen (94% vs 69% ,P = .01). Disease status at HCT, androgen use, number of malformations, recipient age and gender, mosaicism, and history of prior infections did not have a demonstrable effect on neutrophil recovery. In multivariate analysis, factors associated with improved neutrophil recovery were CMV seronegative serostatus, HLA matched donor-recipient pair and use of FLU (Table 1). Similarly, incidence of platelet recovery (>20,000/uL) was significantly higher in CMV negative recipients (Relative Risk [RR] 2.46, 95% CI 1.16–5.22, P = .02), HLA matched HSC (RR 3.1, 95% CI 1.39–6.82, P = .01), and FLU (RR 10.8, 95% CI 2.82–41.3, P = .01). In summary, hematopoietic recovery after AD HSCT in FA patients following FLU containing preparative regimens are comparable to those of HLA matched sibling donor BM recipients. Therefore significant practice changes should be considered such as the use of a FLU containing preparative regimen, particularly in the setting of TCD.

Table 1. *Cox Regression on Primary Neutrophil Engraftment*

Factors	Relative Risk (95% CI)	*P*-value
Model (X2 = 28.8, *P* < .01)		
Recipient CMV		
Positive*	**1**	
Negative	**1.95 (1.13–3.35)**	**.02**
HLA match		
Mismatch*	**1**	
Match	**2.70 (1.59–4.60)**	**.01**
FLU		
No*	**1**	
Yes	**2.10 (1.22–3.63)**	**.01**

*Note: reference category.

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LACK OF T CELL ALLOREACTIVITY TO CORD BLOOD MONONUCLEAR CELLS

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Transplantation of HLA-mismatched cord blood (CB) nucleated cells has limited risk of graft rejection and severe acute graft-versus-host disease. This may depend on naïve T cells not yet exposed to many antigens and/or on immature antigen-presenting cells (APC) not delivering appropriate signals to allogeneic T cells. In order to test the APC activity of human circulating CB cells in vitro, we initially used irradiated CB mononuclear cells (MNC) or immunomagnetically selected CD34+ cells, CD133+ cells, or CD14+ monocytes to stimulate the proliferative response of incompatible blood T cells in mixed leukocyte culture (MLC). CB MNC failed to induce allogeneic T cell proliferation, while CD34+ and CD133+ progenitors or CD14+ monocytes induced potent T cell alloresponses. Nevertheless, since allogeneic T cell response was not restored after depletion of CD3+ cells in the CB, or the add-back of irradiated CB MNC to CD34+ or CD14+ stimulators inhibited allo-T cells, a direct suppressive effect of CB MNC was excluded. Allogeneic peripheral blood cytotoxic T-lymphocyte (CTL) responses were not induced after 7 days of stimulation with irradiated CB MNC, although after 4 weekly rechallenges with CB MNC, on average a 23% lysis of antigen-specific CB PHA-blasts was observed at the highest effector:target ratio (50:1). To test the tolerogenic potential of CB MNC, T cells initially exposed to CB MNC were rechallenged in secondary MLC with CB MNC, or CD34+ cells, or monocyte-derived dendritic cells (Mo-DC) generated in liquid culture with GM-CSF and IL-4. Allogeneic T cells were still unresponsive upon rechallenge with CB MNC, but proliferated upon 3 days of restimulation with CD34+ cells or Mo-DC from the same CB. These results show an impaired allo-APC activity of CB MNC but not CB CD34+ cells, and suggest that although CB cells do not induce an Ag-specific in vitro anergy, their weak APC activity may reduce the risk of rejection in an HLA-mismatched stem cell transplant setting. In addition, these findings may explain the initial engraftment of two mismatched CB grafts, currently infused in CB transplant protocols for adult patients.

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NO ASSOCIATION BETWEEN MIC-A POLYMORPHISM AND CLINICAL OUTCOME AFTER ALLOGENEIC HSCT

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Background: MHC class I chain related molecule A (MIC-A) shows homology with the classical HLA molecules. MIC-A is polymorphic with more than 50 recognized alleles and is described as a "marker of stress" since it is up-regulated on epithelial cells at heat and virus infection. The presence of MIC-A antibodies in patient sera has been associated with rejection after organ transplantation. The significance of MIC-A polymorphism in hematopoietic stem cell transplantation (HSCT) has not been studied. In this study we wanted to see the degree of MIC-A mismatch between patients and donors and to investigate if the MIC-A genotype was associated with clinical outcome after HSCT. **Materials and Methods:** For MIC-A genotyping, we performed PCR amplification with allele-specific primers. A total of 248 leukemia patients were included in the study. All received myeloablative conditioning and GVHD prophylaxis consisted mainly of a combination of cyclosporine A and methotrexate. In unrelated transplants (149), both the patient and the donor were genotyped while in sibling transplants (99) only the patient was genotyped. **Results:** In unrelated transplants, 16 (11%) mismatches were found. Although an increase in the incidence of chronic GVHD was found among patients receiving a graft with MIC-A mismatch, there were no significant differences in leukemia free survival (LFS), transplant related mortality (TRM) and GVHD between patients with MIC-A match or mismatch. At the MIC-A allele level, no specific allele was found to be associated with different clinical outcomes after HSCT. **Conclusion:** MIC-A mismatch is a rare event in HLA matched HSCT. Neither the MIC-A mismatch nor the MIC-A alleles seem to have a major effect on the clinical outcome after HSCT.

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HSCT FROM PARTIALLY MATCHED ALTERNATIVE DONORS—A SINGLE CENTRE EXPERIENCE

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Increased amount of indications for alloBMT is connected with increased demand for donors. For approximately 30% of the patients is possible to find HLA identical sibling, for another 70% of the patients is necessary to obtain graft from alternative donors. Because it can be difficult or even impossible to find fully matched alternative donors, that means donors identical in all 10 HLA antigens typed on HR level of A, B, C, DRB1, and DQB1 loci, we must often accept donors with some mismatches. We performed 182 transplantations from alternative donors between 1991 and 2005. 89 were mismatched for one or more HLA alleles or antigens. Twenty-nine patients were transplanted for AML, 26 for CML, 12 for ALL, 10 for MDS, 4 for CLL, 3 for MMM, 2 for NHL, 2 for HD, and 1 for MM. Half of these patients were transplanted in advanced stage of the disease. In 80% of the patients, ATG-Fresenius was used in conditioning and 17% of the

patients were transplanted without serotherapy. The most frequent mismatch in our cohort of the patients was single mismatch on C locus (28%), followed by combined mismatch in class I and II (24%). Multiple mismatch in class I was present in 19% and 1 single mismatch on A or B loci in 8% of the patients. Seven percent of the patients received graft with 2 mismatches on C, while 7% received graft with 1 and 7% with multiple mismatch in class II HLA. **Results:** 34 patients developed GVHD (Gr I-38%, Gr II-38%, Gr III-12%, and Gr IV-12%). Forty-one patients died after BMT; 40% for relapse, 31% for infection, 18% for GVHD, and 11% due to VOD. Three year probability of survival is 40% for AML, 60% for CML, 75% for ALL, and 30% for MDS patients. Three-year probability of survival of the 17 patients, 14 of whom in advanced stage of the disease, who received graft mismatched for DRB1, is 50%. **Summary:** BMT from partially matched alternative donors offer chance for the patients without fully (10/10) matched donor. ATG in conditioning decreases the risk of severe GVHD (24% Gr III+IV). Relapse and infection were the most common causes of treatment failure in our cohort of the patients.

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A SYSTEMATIC REVIEW AND META ANALYSIS OF UNRELATED DONOR UMBILICAL CORD BLOOD TRANSPLANTATION VERSUS UNRELATED DONOR BONE MARROW TRANSPLANTATION IN ADULT AND PEDIATRIC PATIENTS

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Several studies have been performed to compare the results of unrelated donor bone marrow transplantation (UBMT) with unrelated donor cord blood transplantation (UCBT). In order to objectively analyze these data, we performed a systematic review and meta analysis of pooled data on comparative studies on unrelated donor BMT versus UCBT to evaluate if UCBT is equivalent to BMT in patients requiring a haematopoietic stem cell transplant. Combining the studies, 161 children and 331 adults undergoing UCBT (mostly 1-2 antigen mismatched), as well as 316 children and 646 adults undergoing UBMT (almost entirely fully matched with the recipient) were analyzed. Post-transplant engraftment of neutrophils and platelets occurred slower and more infrequently with UCBT, although the difference was only in the order of 10–20%. Two to 3 year overall survival was equivalent in children undergoing UCBT (35 to 59%) compared to those who had matched unrelated donor BMT (41 to 57%). In pooled comparisons of the studies between UCBT and UBMT in children, chronic graft-versus-host disease (GVHD) was less with UCBT (pooled estimate 0.26, CI 0.12–0.57, $P = .0007$) although grade III–IV acute GVHD (pooled estimate1.46, CI 0.42–5.03) was no different. There was a trend towards lower overall mortality in children undergoing UCBT (pooled estimate 2.12, CI 0.94–4.77, $P = .07$). For adults, relapse rates (pooled estimate 0.86, CI 0.62–1.19), transplant related mortality (pooled estimate 1.04, CI 0.52–2.08) and disease free survival (pooled estimate 0.59, CI 0.18–1.96) were not statistically different. In conclusion, pooled analysis of comparative studies in children and adults revealed that 1-2 antigens mismatched UCBT had consistently equivalent survival outcomes when compared with fully matched unrelated donor BMT.

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UNMANIPULATED HLA 2-3 ANTIGEN-MISMATCHED (HAPLOIDENTICAL) NONMYELOABLATIVE STEM CELL TRANSPLANTATION

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To expand the donor pool, allogeneic stem cell transplantation (SCT) using HLA 2-3 antigen-mismatched (haploidentical) related donors has been studied. To date, there are a few reports describing nonmyeloablative stem cell transplantation (NST) from HLA-haploidentical donors. We recently showed that a nonmyeloablative regimen consisting of fludarabine, busulfan, and ATG was sufficiently immunosuppressive to achieve donor type engraftment in transplantation from HLA-haploidentical donors who had 1 antigen-mismatch in the GVH direction and 2-3 antigen-mismatches in the HVG direction (Leukemia, 2003). In that study, however, acute GVHD could not be sufficiently controlled with a GVHD prophylaxis using cyclosporine or tacrolimus. We have been testing a protocol for HLA-haploidentical NST from 2-3 antigen-mismatched donors in the GVH direction without T-cell depletion using more intensified GVHD prophylaxis (tacrolimus and methylprednisolone). **Methods:** We performed an HLA-haploidentical NST from 2-3 antigen-mismatched donors in the GVH direction. Between Jan 2000 and July 2005, 30 patients with hematologic malignancies, including AML, ALL, CML, and NHL, underwent allogeneic SCT in Osaka University Hospital. The median age of the patients was 50 (range 28–63). All patients except for 3 patients with Philadelphia chromosome were in advanced stage at the time of transplantation. Four patients had a prior autologous SCT, and all of them underwent HLA-haploidentical NST because of recurrence of the original disease. Preconditioning regimen consists of fludarabine (30 mg/m^2 $\times$ 6), busulfan 4 mg/kg $\times$ 2, and rabbit ATG (Fresenius) 2 mg/kg $\times$ 4. GVHD prophylaxis regimen consists of tacrolimus 0.02 mg/kg/day and methylprednisolone 1 mg/kg/day from day 0. **Results:** All patients except for one achieved donor type engraftment. The patient who had a rejection was successfully rescued with second transplantation from the same donor. Fifteen patients did not develop acute GVHD clinically, and only 5 patients developed grade II GVHD. The main causes of death were relapse and thrombotic microangiopathy. The overall survival at 3 years was 49.2 % at a median follow-up of 664 days (range, 37–1918 days). **Conclusions:** HLA-haploidentical NST may be feasible for patients who are at high risk and lack available donors, and who are considered ineligible for myeloablative regimens because of advanced age or comorbidities, although our results have to be confirmed in a large-scale study.

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THE IMPACT OF HLA-B ALLELE LEVEL MATCHING ON UNRELATED STEM CELL DONOR TRANSPLANTS IN GERMANY

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The German Consensus for matching allogeneic donors of hematopoietic progenitor cell (1996/2000) recommends matching donors for HLA-A,B on serological level (2 digit allele level matching within split groups for B15, B40) and by allele level for DRB1 and, if possible, DQB1. We have retrospectively performed sequencing based HLA-A,B,C analyses for 262 adult unrelated donor recipient pairs matching for A, B, and DRB1 according to the above definition in order to see if outcome could be improved by more stringent selection criteria. Accepted diagnoses were ALL (21%), AML (39%), CML (33%), and MDS (7%). Sixty percent of the patients were male with a median age of 38 (range 18–67) whereas 67% of the donors were male with a median age of 36 (range 19–58). The patients were transplanted in Berlin (56), Erlangen (6), Hannover (9), Heidelberg (18), Mainz (56), Munich (50), Regensburg (13), Ulm (11), and Wiesbaden (43) using heterogeneous regimens for conditioning and GvHD-prophylaxis. After analyzing the relevant covariates, we stratified the Cox proportional hazard model for patient age (< > median), diagnosis, and disease phase (early 145, advanced 117). We found 20 pairs with an allele level difference for A, 43 for B, 112 for C, and 20 for DQB1. The only significant detrimental effect for survival was seen for allele level differences of HLA-B with R = 1.56 (1.01 . . . 2.41) and $P < .05$. The survival curves did not suggest an influence of any other HLA difference mentioned except for advanced disease where allele differences of HLA-A or C may be beneficial, probably due to a GvL effect. Study supported by the German José Carreras Leukemia Foundation.